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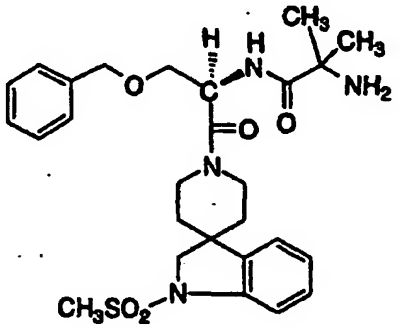
(54) Title: PROCESS FOR THE PREPARATION OF A GROWTH HORMONE SECRETAGOGUE

(57) Abstract

The present invention is directed to a novel process for the preparation of the compound N-[1(R)-{(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methyl-propanamide, and salts thereof, which has structure (1) and which has the ability to stimulate the release of natural or endogenous growth hormone. This compound may be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal.



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TITLE OF THE INVENTION

PROCESS FOR THE PREPARATION OF A GROWTH HORMONE SECRETAGOGUE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

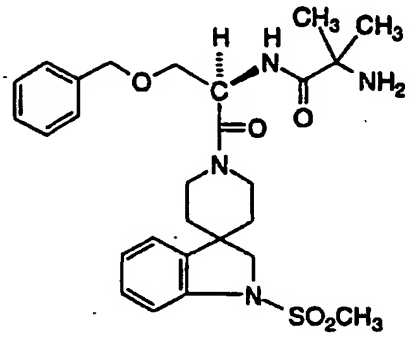
Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which

must be given by injection or by a nasal spray. Other compounds have been developed which stimulate the release of endogenous growth hormone.

In particular, certain spiro compounds are disclosed in PCT Patent Publication WO 94/13696 and Proc. Natl. Acad. Sci. USA, 92, 7001-7005 (July 1995) as being non-peptidal growth hormone secretagogues. These compounds have the ability to stimulate the release of natural or endogenous growth hormone and thus may be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal.

Among the preferred compounds disclosed therein is spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methylpropanamide which has the structure:

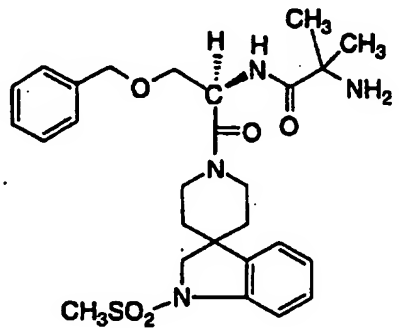


PCT Patent Publication WO 94/13696 discloses methods for preparing this compound (see Examples 18, 19 and 55). However, the synthesis of the compound was accomplished by using the very expensive amino acid coupling agent EDC ($1100/kg); the use of numerous equivalents of trifluoroacetic acid as the catalyst for the BOC group deprotections; extensive chromatographic purifications; and resulted in "gumming" of the final product.

The advantages of the present invention include: a 6-step high yielding non-isolation process providing material of ≥99.9% purity; decreased expense through the use of DCC [$40/kg] instead of EDC [$1100/kg]; diminished environmental impact through the use of methanesulfonic acid instead of trifluoroacetic acid as the catalyst (as well as lesser equivalents of catalyst) in the deprotections; and ease of isolation of the final product.

SUMMARY OF THE INVENTION

The instant invention is directed to a process for the preparation of the compound N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methyl-propanamide which has the structure:

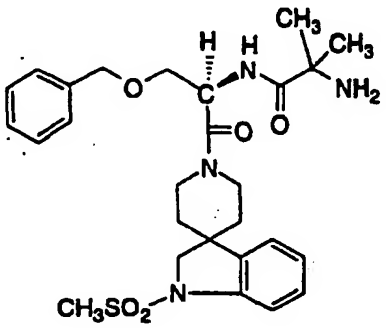


and salts thereof, in particular, the methanesulfonate salt.

This compound has the ability to stimulate the release of natural or endogenous growth hormone and may be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal.

DESCRIPTION OF THE INVENTION

The present invention is directed to a novel process for the preparation of the compound N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methyl-propanamide which has the structure:

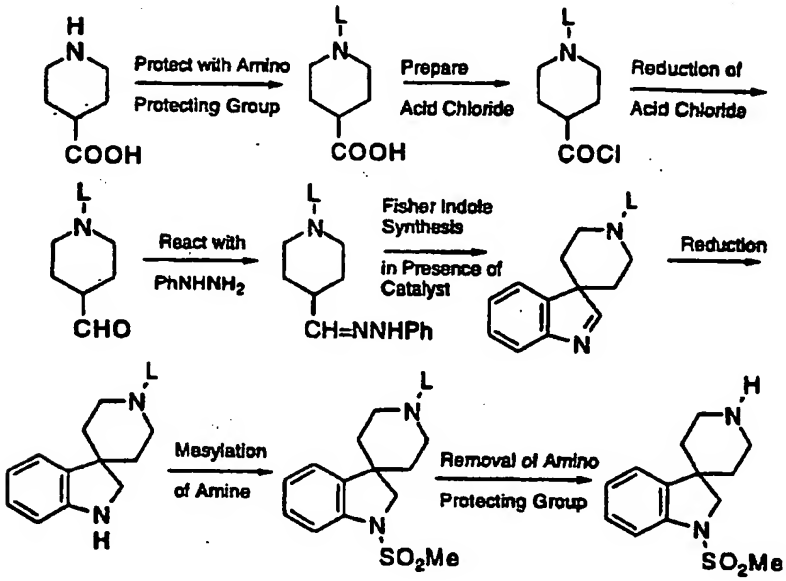


and salts thereof, in particular, the methanesulfonate salt.

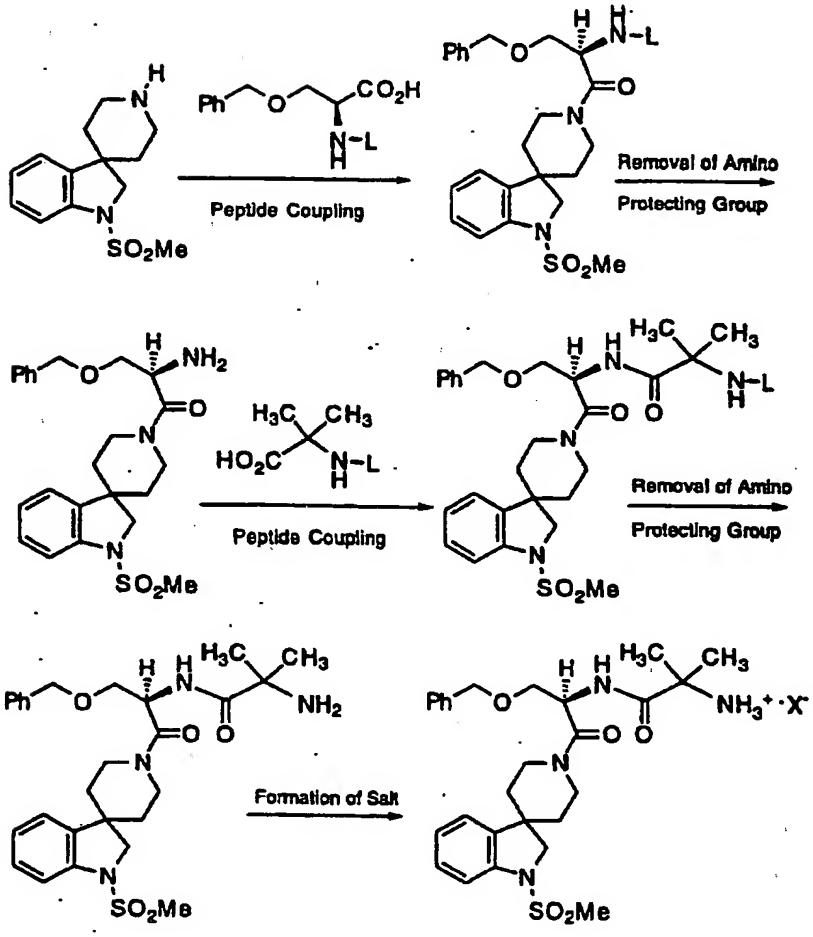
The instant process provides the desired compound from readily available inexpensive and environmentally acceptable starting materials reagents and solvents. The process does not require the use any chromatographic purifications, and it is possible to produce the final product from the intermediate spiroindoline sulfonamide without isolation of any of the intermediates.

The individual processes within the general process are summarized as follows:

SCHEME I

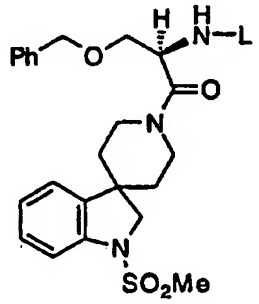


SCHEME I (CONT'D)



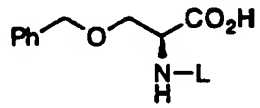
(wherein L is an appropriate amino protecting group and X^- is an appropriate counterion).

Within this general process, a first process concerns the preparation of a compound of formula I:

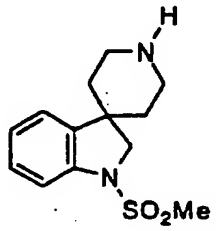


I

wherein L is an amino protecting group, by coupling an amino acid of the formula:



with a compound of the formula :



in the presence of an acid activating agent in an inert solvent in the presence of a catalytic agent, to give the compound of formula I.

Acid activating agents suitable for this process include: DCC, EDC, ECAC and BOP, in which the preferred acid activating agent is DCC (N,N'-dicyclohexylcarbodiimide).

Catalytic agents suitable for this process include: HOBT and the like in which a preferred catalytic agent is HOBT (hydroxybenzotriazole).

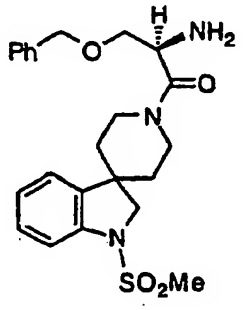
Inert solvents appropriate for this processes include: acetonitrile; iso-propyl acetate; ethyl acetate; propionitrile; water; chlorinated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, ortho-dichlorobenzene; benzene; toluene; xylenes; and the like; and mixtures thereof, in which the preferred solvent is either acetonitrile or isopropyl acetate and water.

The preferred reaction temperature range is between -40 and 150°C, and the most preferred range is between 20 and 35°C.

Suitable amino protecting groups include: benzyl, benzyloxymethyl, benzyloxycarbonyl (carbobenzyloxy), benzylsulfonyl, 2-bromo-ethyloxycarbonyl, t-butoxy-carbonyl, 2-chloro-benzyloxy-carbonyl, 2-chloroethyloxycarbonyl, di-t-amyloxycarbonyl, 9-fluoroenyl-methyloxycarbonyl, isopropoxycarbonyl, 4-methoxy-benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrophenyl-sulfonyl, phthaloyl, 2,2,2-trichloro-t-butyloxycarbonyl, trifluoroacetyl, triphenylmethane, allyloxycarbonyl, and vinyloxycarbonyl groups, and the like, in which the preferred ones include benzyloxycarbonyl (carbobenzyloxy), t-butoxy-carbonyl groups, and in which the most preferred one is the t-butoxy-carbonyl group.

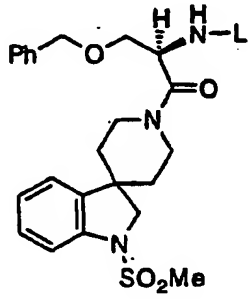
In the interest of efficiency, it is preferred that this coupling be conducted *in situ* without isolation of the compound of formula I following its preparation by the aforementioned process.

Within this general process, a second process concerns the preparation of a compound of formula II:



II

which comprises reacting a compound of the formula I:



I

wherein L is an amino protecting group, with an amino deprotecting agent to give the compound of formula II.

Suitable amino protecting groups include: benzyl, benzyloxymethyl, benzyloxycarbonyl (carbobenzyloxy), benzylsulfonyl, 2-bromo-ethyloxycarbonyl, t-butoxy-carbonyl, 2-chloro-benzyloxy-carbonyl, 2-chloroethyloxycarbonyl, di-t-amyloxycarbonyl, 9-fluoroenyl-methyloxycarbonyl, isopropoxycarbonyl, 4-methoxy-benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrophenyl-sulfonyl, phthaloyl, 2,2,2-trichloro-t-butyloxycarbonyl, trifluoroacetyl, triphenylmethane, allyloxycarbonyl, and vinyloxycarbonyl groups, and the like, in which the preferred ones include benzyloxycarbonyl (carbobenzyloxy), t-butoxy-

carbonyl groups, and in which the most preferred one is the t-butoxy-carbonyl group.

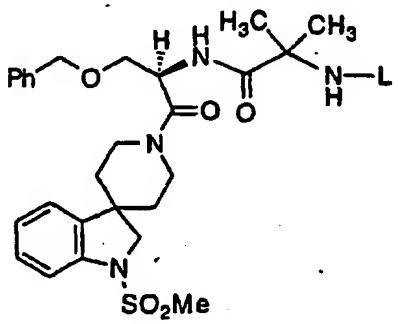
In this process, the removal of the amino protecting group may be accomplished by use of an appropriate catalytic agent. Removal of a t-butoxycarbonyl protecting group may be carried out in a solvent such as methanol, ethanol, methylene chloride, ethyl acetate, or isopropyl acetate, with a strong acid. Such strong acids include methanesulfonic acid, trifluoroacetic acid, hydrochloric acid, hydrogen chloride gas, hydrogen bromide; hydrogen iodide; trifluoromethane-sulfonic acid; camphorsulfonic acid; sulfuric acid; phosphoric acid; and an arylsulfonic acid, such as benzenesulfonic acid, p-toluenesulfonic acid, and p-chlorobenzene-sulfonic acid. Preferred catalytic agents include: trifluoroacetic acid; methanesulfonic acid; camphorsulfonic acid; benzenesulfonic acid, p-toluenesulfonic acid; and p-chlorobenzene-sulfonic acid. The most preferred catalytic agent is methanesulfonic acid. The preferred solvent is methanol or ethanol, and the most preferred solvent is ethanol.

The preferred reaction temperature range is between -40 and 150°C, and the most preferred range is between 10 and 40°C.

Removal of a benzyloxycarbonyl (carbobenzyloxy) group may be achieved by a number of methods, for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, the removal of benzyloxycarbonyl (carbobenzyloxy) group may also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide.

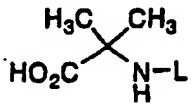
In the interest of efficiency, it is preferred that this acid-catalyzed deprotection be conducted *in situ* without isolation of the compound of formula II following its preparation by the aforementioned process.

Within this general process, a third process concerns the preparation of a compound of formula III:

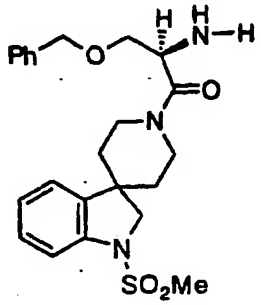


III

wherein L is an amino protecting group, by coupling an amino acid of the formula:



wherein L is an amino protecting group, with a compound of the formula II:



II

in the presence of an acid activating agent in an inert solvent in the presence of a catalytic agent, to give the compound of formula III.

Acid activating agents suitable for this process include:

DCC, EDC, ECAC and BOP, in which the preferred acid activating agent is DCC (N,N'-dicyclohexylcarbodiimide).

Catalytic agents suitable for this process include: HOBT and the like in which a preferred catalytic agent is HOBT (hydroxybenzotriazole).

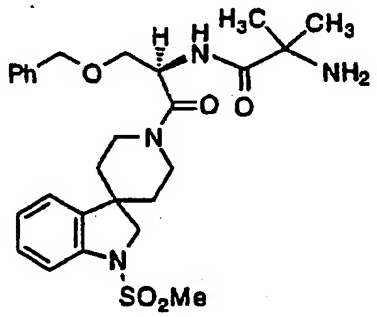
Inert solvents appropriate for this processes include: acetonitrile; isopropyl acetate; ethyl acetate; propionitrile; water; chlorinated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride; dichloroethane, chlorobenzene, ortho-dichlorobenzene; benzene; toluene; xylenes; and the like; and mixtures thereof, in which the preferred solvent is a mixture of iso-propyl acetate and water, preferably in a ratio of approximately 40:60 to 60:40 (by volume) and more preferably in a ratio of approximately 50:50 (by volume).

The preferred reaction temperature range is between -40 and 150°C, and the most preferred range is between 20 and 50°C.

Suitable amino protecting groups include: benzyl, benzyloxymethyl, benzyloxycarbonyl (carbobenzyloxy), benzylsulfonyl, 2-bromo-ethyloxycarbonyl, t-butoxy-carbonyl, 2-chloro-benzyloxy-carbonyl, 2-chloroethyloxycarbonyl, di-t-amyloxycarbonyl, 9-fluoroenyl-methyloxycarbonyl, isopropoxycarbonyl, 4-methoxy-benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrophenyl-sulfonyl, phthaloyl, 2,2,2-trichloro-t-butyloxycarbonyl, trifluoroacetyl, triphenylmethane, allyloxycarbonyl, and vinyloxycarbonyl groups, and the like, in which the preferred ones include benzyloxycarbonyl (carbobenzyloxy), t-butoxy-carbonyl groups, and in which the most preferred one is the t-butoxy-carbonyl group.

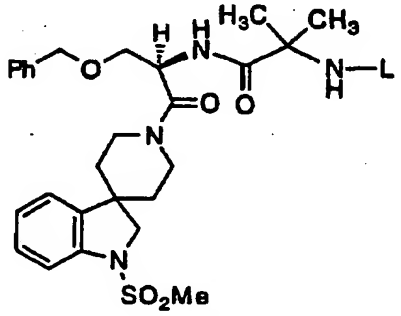
In the interest of efficiency, it is preferred that this coupling be conducted *in situ* without isolation of the compound of formula III following its preparation by the aforementioned process. Alternatively, the compound of formula III may be isolated as a discrete intermediate.

Within this general process, a fourth process concerns the preparation of a compound of formula IV, or a pharmaceutically acceptable salt thereof:



IV

which comprises reacting a compound of the formula III:



III

wherein L is an amino protecting group, with an amino deprotecting agent to give the compound of formula IV.

Suitable amino protecting groups include: benzyl, benzyloxymethyl, benzyloxycarbonyl (carbobenzyloxy), benzylsulfonyl, 2-bromo-ethyloxycarbonyl, t-butoxy-carbonyl, 2-chloro-benzyloxy-carbonyl, 2-chloroethyloxycarbonyl, di-t-amyloxycarbonyl, 9-fluoroenyl-methyloxycarbonyl, isopropoxycarbonyl, 4-methoxy-benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrophenyl-sulfonyl, phthaloyl, 2,2,2-trichloro-t-butyloxycarbonyl, trifluoroacetyl, triphenylmethane,

allyloxycarbonyl, and vinyloxycarbonyl groups, and the like, in which the preferred ones include benzyloxycarbonyl (carbobenzyloxy), t-butoxy-carbonyl groups, and in which the most preferred one is the t-butoxy-carbonyl group.

In this process, the removal of the amino protecting group may be accomplished by use of an appropriate catalytic agent. Removal of a t-butoxycarbonyl protecting group may be carried out in a solvent such as methanol, ethanol, methylene chloride, ethyl acetate, or iso-propyl acetate, with a strong acid. Such strong acids include methanesulfonic acid, trifluoroacetic acid, hydrochloric acid, hydrogen chloride gas, hydrogen bromide; hydrogen iodide; trifluoromethane-sulfonic acid; camphorsulfonic acid; sulfuric acid; phosphoric acid; and an arylsulfonic acid, such as benzenesulfonic acid, p-toluenesulfonic acid, and p-chlorobenzene-sulfonic acid. Preferred catalytic agents include: trifluoroacetic acid; methanesulfonic acid; camphorsulfonic acid; benzenesulfonic acid, p-toluenesulfonic acid; and p-chlorobenzene-sulfonic acid. The most preferred catalytic agent is methanesulfonic acid. It is preferred that compound of formula V is isolated in the form of the methanesulfonate salt. The preferred solvent is methanol or ethanol, and the most preferred solvent is ethanol.

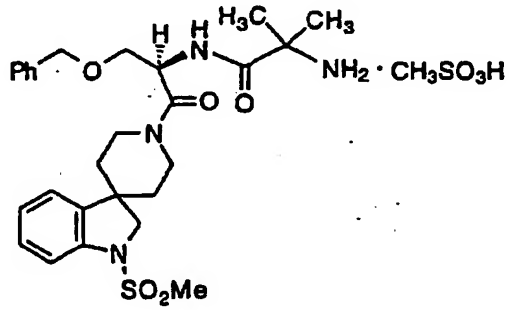
The preferred reaction temperature range is between -40 and 150°C, and the most preferred range is between 10 and 40°C.

Removal of a benzyloxycarbonyl (carbobenzyloxy) group may be achieved by a number of methods, for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, the removal of benzyloxycarbonyl (carbobenzyloxy) group may also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide.

In the interest of efficiency, it is preferred that this acid-catalyzed deprotection be conducted *in situ* without isolation of the

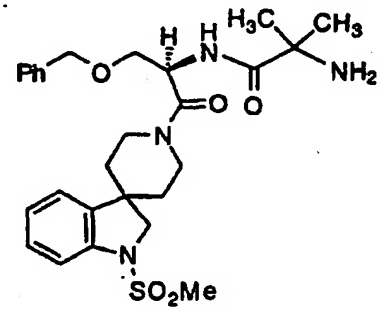
compound of formula IV following its preparation by the aforementioned process.

Within this general process, a fifth process concerns the preparation of a pharmaceutically acceptable salt of a compound of formula IV, in particular, the methanesulfonate salt, i.e. a compound of formula V:



V

which comprises reacting a compound of the formula IV:



IV

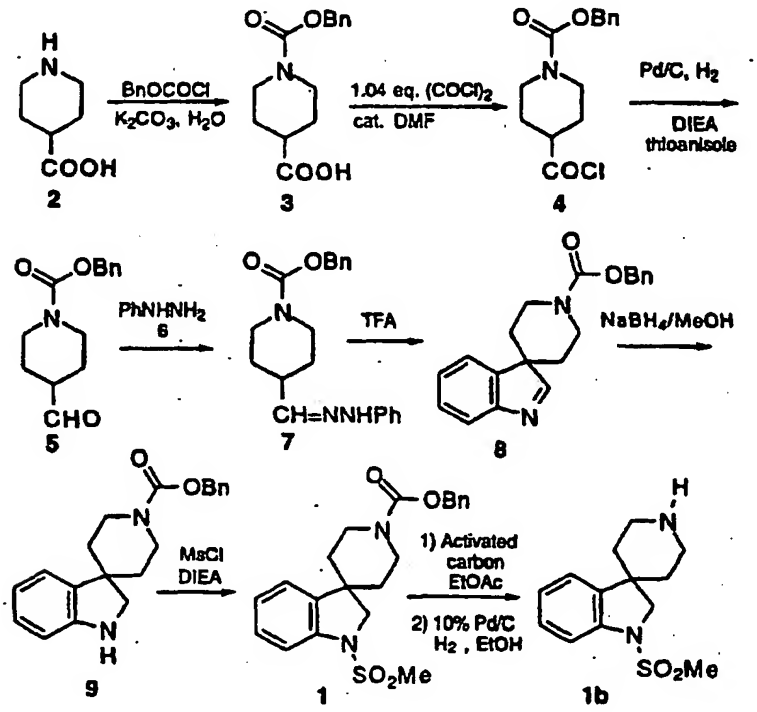
with an acid, preferably methanesulfonic acid, to give the compound of formula V.

It is preferred that compound of formula V is isolated in the form of the methanesulfonate salt. The preferred solvent comprises ethyl acetate and ethanol, and the most preferred solvent is a mixture of ethyl acetate and ethanol.

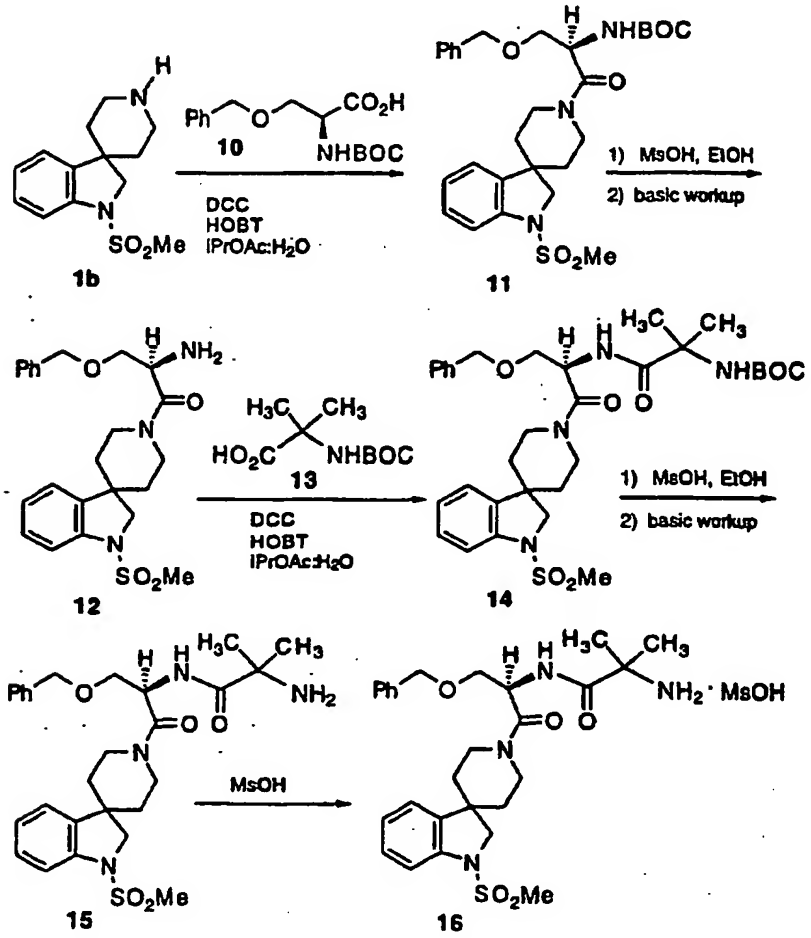
In the interest of efficiency, it is preferred that the formation of the salt be conducted *in situ* without isolation of the compound of formula V following its preparation by the aforementioned process.

In a preferred embodiment of the present invention, the individual processes within the general process are outlined as follows:

SCHEME II:



SCHEME II (CONT'D)



In this preferred embodiment, the CBZ-Spiroindoline 1 is treated with Darco (20% by weight) prior to hydrogenation. The hydrogenation is carried out in ethanol at 65°C over 10% Pd/C with vigorous stirring.

A solution of 1b in isopropyl acetate and water is coupled with commercially available N-BOC-O-benzyl-D-serine in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt). After filtration of the dicyclohexylurea (DCU) side product, the 2-phase filtrate is separated and the organic layer is washed successively with 1M aqueous sodium hydroxide solution, 0.5M aqueous hydrochloric acid and finally saturated aqueous sodium hydrogen carbonate. Improved results in this coupling are achieved when a solution of the free amino in iPrOAc/H_2O is treated with DCC, HOBT followed by addition of the amino acid at ambient temperature and followed by reaction for 3-5 hrs The batch is then concentrated *in vacuo* and the solvent is switched from isopropyl acetate to ethanol. This solvent switch generally proceeds swiftly by "feeding and bleeding" 3x batch volumes to remove isopropyl acetate..

The BOC-group of 11 is removed by treatment with methanesulfonic acid (MsOH) (3 eq) in ethanol at 35-40°C. Partitioning between isopropyl acetate and aqueous 1M sodium hydroxide solution affords 12.

The coupling of 12 with N-BOC-α-aminoisobutyric acid is best conducted in a two-phase solvent system, isopropyl acetate/water (1:1) in the presence of DCC and HOBt (1.1 eq. each). Removal of the DCU by filtration, separation of the layers and washing the organic layer successively with 1M aqueous sodium hydroxide, 0.5M aqueous hydrochloric acid and saturated aqueous sodium hydrogen carbonate affords 14.

The mixture is solvent switched to ethanol for the subsequent methanesulfonic acid cleavage of the Boc group. Deprotection of 14 is more difficult than that of 11 and requires a concentrated solution of ethanol/methanesulfonic acid and heating to 35-40°C. After extractive workup (EtOAc-NaOH), the free amine 15 is

isolated. The organic layer is washed well with 1N NaOH to ensure complete removal of methanesulfonic acid.

The ethyl acetate solution of the free base 15 is concentrated to low bulk *in vacuo* and is azeotroped dry (KF <500 $mgml^{-1}$) by "feeding and bleeding" 2x batch volumes of 90/10, ethyl acetate/ethanol followed by 2x batch volumes of ethyl acetate. The resulting dry, slightly hazy solution of the free base 15 in ethyl acetate is treated with Darco G-60 (25 weight %) at room temperature for about 10 hours. Removal of the Darco by filtration with a filtration agent gives the free base 15.

Formation of the methanesulfonic acid salt 16 from 15 is carried out in EtOAc with 1.1 eq of MsOH at about 50°C. The free base 15 is treated with 8 volume % of EtOH and 1 eq of H_2O and heated to 55°C until complete dissolution. Cooling to ambient temperature and stirring the resulting slurry for 4 hours gives crystalline material of 16 designated as crystal Form II [solubility in IPA = 12 mg/mL].

The conversion of Form II to Form I is accomplished where the salt is formed in EtOAc-EtOH as above, but instead of cooling the initial solution of the salt (at 55°C) to ambient temperature, it is cooled to 45°C. Crystals should start appearing at that temperature and the slurry should become thicker with time. The temperature is then raised to 51°C and the slurry is aged overnight. Complete conversion to Form I of 16 should be expected.

Preferably, the conversion of Form II to Form I is achieved by adding seed crystals of Form I to a solution of the free base in EtOAc-EtOH at 50-55°C followed by aging. Accordingly, the free base 15 may be treated with 1.1 equivs. of methanesulfonic acid in 8% ethanol in ethyl acetate at 50-55°C. The batch is then seeded with approximately 2% by weight of Form I of the methanesulfonate salt 16, and then aged at 55°C overnight. The batch is cooled to room temperature and aged for approximately 2-3 hours. The product is isolated by filtration at room temperature under a nitrogen atmosphere, dried at 35°C *in vacuo* and sieved to give the methanesulfonate salt 16.

The methanesulfonic acid salt 16 may also be formed by alternating the stepwise addition of MsOH (1.1 eq) and seed crystals of

Form I to a solution of the free base in EtOAc-EtOH at about 50°C, wherein the order of addition of the MsOH and the seed is not critical.

Throughout the instant application, the following abbreviations are used with the following meanings:

Bu	butyl
Bn	benzyl
BOC, Boc	t-butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tris(dimethylamino)-phosphonium hexafluorophosphate
calc.	calculated
CBZ, Cbz	Benzyloxycarbonyl
DCC	N,N'-Dicyclohexylcarbodiimide
DIEA	Di-isopropylethylamine
DMF	N,N-dimethylformamide
DMAP	4-Dimethylaminopyridine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDAC	Ethyl-3-(3-dimethylamino)-propylcarbodiimide
EI-MS	Electron ion-mass spectroscopy
Et	ethyl
eq.	equivalent(s)
FAB-MS	Fast atom bombardment-mass spectroscopy
h, hr.	hours
HOBT, HOBt	Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
iPrOAc	iso-Propyl acetate
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MF	Molecular formula
MHz	Megahertz
MPLC	Medium pressure liquid chromatography
MsOH	Methane sulfonic acid

NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
Ph	phenyl
Pr	propyl
prep.	prepared
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The phrase "peptide coupling reaction" as used herein is intended to mean the coupling of a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in an inert solvent in the presence of a catalyst such as HOBT. Inert solvents appropriate for such couplings include: acetonitrile; iso-propyl acetate; ethyl acetate; propionitrile; water; chlorinated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, ortho-dichlorobenzene; benzene; toluene; xylenes; and combinations thereof; and the like.

The variable "L" and the term "amino protecting group" is intended to indicate the presence of an appropriate protecting group for amino, such as those described in Greene, T.W., Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991. An appropriate protecting group will be able to withstand the reaction conditions of intermediate processes, prior to being removed when desired. The amino protecting group is independently selected for each process within the entire processes.

Suitable amino protecting groups include: benzyl, benzyloxymethyl, benzyloxycarbonyl (carbobenzyloxy), benzylsulfonyl, 2-bromo-ethyloxycarbonyl, t-butoxy-carbonyl, 2-chloro-benzyloxy-carbonyl, 2-chloroethyloxycarbonyl, di-t-amyloxycarbonyl, 9-fluoroenyl-methyloxycarbonyl, isopropoxycarbonyl, 4-methoxy-benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrophenyl-sulfonyl, phthaloyl, 2,2,2-

trichloro-t-butyloxycarbonyl, trifluoroacetyl, triphenylmethane, and vinyloxycarbonyl groups, and the like, in which the preferred ones include benzyloxycarbonyl (carbobenzyloxy), t-butoxy-carbonyl groups, and in which the most preferred one is the t-butoxy-carbonyl group.

The removal of the amino protecting group may be accomplished by use of an appropriate catalytic agent. Removal of a t-butoxycarbonyl protecting group may be carried out in a solvent such as methanol, ethanol, methylene chloride, ethyl acetate, or iso-propyl acetate, with a strong acid. Such strong acids include methanesulfonic acid, trifluoroacetic acid, hydrochloric acid, hydrogen chloride gas, hydrogen bromide; hydrogen iodide; trifluoromethane-sulfonic acid; camphorsulfonic acid; sulfuric acid; phosphoric acid; and arylsulfonic acids, such as benzenesulfonic acid, p-toluenesulfonic acid, and p-chlorobenzene-sulfonic acid. Preferred catalytic agents include: trifluoroacetic acid; methanesulfonic acid; camphorsulfonic acid; benzenesulfonic acid, p-toluenesulfonic acid; and p-chlorobenzene-sulfonic acid. The most preferred catalytic agent is methanesulfonic acid. The preferred solvent is methanol or ethanol.

Removal of a benzyloxycarbonyl (carbobenzyloxy) protecting group may be achieved by a number of methods, for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, the removal of benzyloxycarbonyl (carbobenzyloxy) group may also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide.

The amine compounds employed as starting materials for the process of the present invention may be present as their acid salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. Similarly the compounds produced by the processes of the instant invention may be isolated in the form of their pharmaceutically

acceptable acid salts. In addition, certain compounds containing an acidic function such as a carboxy can be in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The preparation of compounds with the process of the present invention may be carried out in sequential or convergent synthetic routes. It is noted that in some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. In general, the process of the present invention is conducted in a sequential manner as presented herein.

Many of the starting materials are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures include crystallization, normal phase or reverse phase chromatography.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.